IPER Claims 1-58

For examination purposes, these claims should be substituted for the originally filed international claims 1-65.

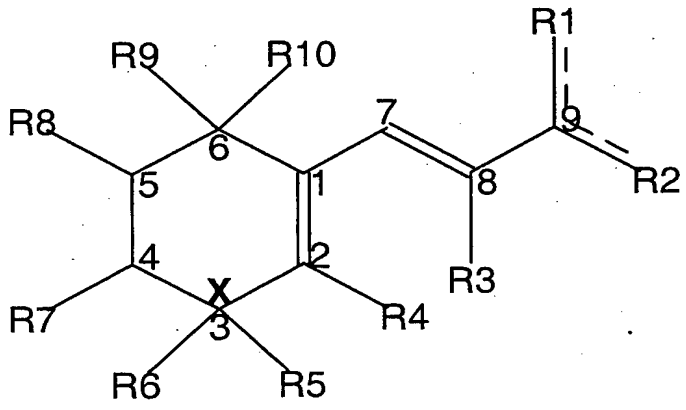
Claims

1. Use of at least one compound capable of inhibiting the visual cycle in an individual in the manufacture of a medicament for prevention or treatment of, in a mammal.

2. Use according to claim 1, wherein said mammal is a human being.

3. Use according to any of claims 1 and 2, wherein said mammal has been diagnosed with diabetes.

4. Use according to any of the preceding claims, wherein the at least one compound comprises a compound of the formula I:

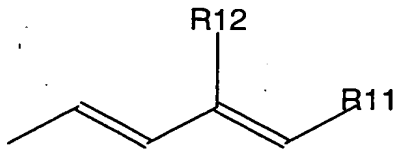


(formula I)

wherein R1 is:

- a lower alkyl, preferably CH2CH3 or CH3, having a single bond to the carbon at position 9 (C9), wherein the bond between C9 and R2 preferably is a double bond, or
- CH2OH or CHO or CF3, or
- CH2 with a double bond to C9, or
- a bond from C9 to R2, or
- OH

and wherein R2 is:



(formula II)

wherein R11 is selected from the group consisting of:

- an alcohol group, such as -CH2OH,
- an aldehyde group, such as -CHO,
- carboxy (-COOH),
- a lower alkyl group, such as -CH3,
- an ether group, such as -CH2OCH3, -CH2OC4H9, -CH2OC6H5 or -CH2OC8H17,
- an ester group, such as -CH2OCOCH3,
- a amine derivative, such as -CH2NHCOCH3, -CH2NHCOC6H5, or -CH2NCH3COCH3,

-CH3COC6H5,

-CH=NOH,

-CH=NNHCOCH3,

-CH=C(COCH2CH2CH3)2,

-CH=C(COCH2)2,

-CH=C(COCH2)2CH2CH=C(COCH2CH2)2CH2,

-COOCH3,

-COOCH2H5,

-COZ, wherein Z is an amino acid, such as glycine, leucine, phenylalanine, or tyrosine,

-CONHC2H5,

-CONHC3H7,

-CONH2C2H4OH,

-CONH2C3H6OH,

-CONH3C3H6OH,

-CONHC6H5,

-CONH2C6H4OH,

-CONH4C6H4OH,

-CONH2C6H4COOH,

-CONH4C6H4COOH,

-CH2OCOCH2Br,

-CH2OCOCH2Cl,

-COOCH2CH3,

- an N-alkylamide group, such as -CONHR, wherein R is an alkyl, preferably 4-hydroxy-phenyl or ethyl,

-COOR, wherein R is beta-D-glucuronide,

- an ethyl sulfone group,

- an ethyl ester group, and

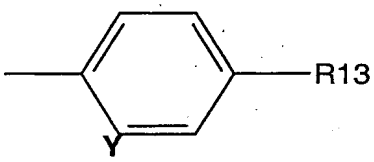
- an alkoxycarbonyl group, such as ethoxycarbonyl

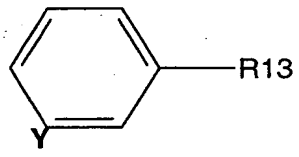
and wherein R12 is:

- a lower alkyl, preferably CH3 or CH2CH3, or

- CH2OH or CHO or CF3,

or R2 is a substituted aryl or heteroaryl, such as:

- 

(formula III) or 

(formula IV)

wherein R13 is selected from the group consisting of:

- carboxy (-COOH),

- an alcohol group, such as -CH2OH,

- an aldehyde group, such as –CHO,

-CH2OCOCH2Br,

-CH2OCOCH2Cl,

-COOCH2CH3,

- a CONHR group, wherein R is an alkyl, preferably 4-hydroxy-phenyl or ethyl),

- COOR, wherein R is beta-D-glucuronide,

- an ethyl sulfone group,

- an ethyl ester group, and

- an alkoxycarbonyl group, such as ethoxycarbonyl;

and wherein Y is C or N or S or O

or R2 is

- O, having a double bond to C9

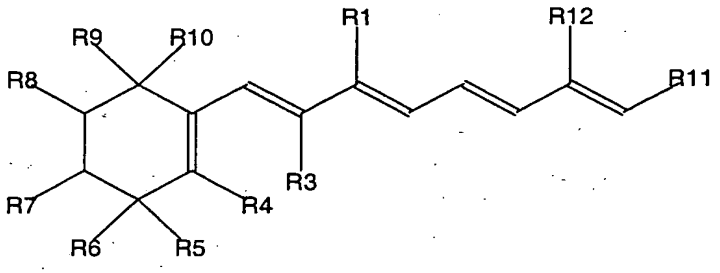
wherein R3 is OH or a lower alkyl or H or CH or CHRCH3 (wherein R is a double bond to R4),
and wherein R4 is H or CH or OH or a lower alkyl, such as CH3,
and wherein R5 is OH or a lower alkyl, such as CH3, or H or O (double bond to atom at position 3) or absent,
and wherein R6 is OH or a lower alkyl, such as CH3, or H or absent or a bond to R5 (if R5 is O) or a bond to C4,
and wherein R7 is alkoxy, such as methoxy, or OH or a lower alkyl, such as CH3, or H or 3-(1-adamantyl)-4-methoxyphenyl,
and wherein R8 is OH or a lower alkyl, such as CH3, or H or a bond to C6,
and wherein R9 is OH or a lower alkyl, such as CH3, or H,
and wherein R10 is OH or a lower alkyl, such as CH3, or H or a bond to C5,
and wherein X is C or N or S or O.

and wherein each of R1, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12 and R13, is optionally substituted one or more times with a lower alkyl group, such as a methyl group or an ethyl group,

with the proviso that when R2 is formula II, and R1, R4, R9 and R12 are all CH3, and R3, R5, R6, R7 and R8 are all H and R11 is a carboxy group, the configuration is not 9-cis (2E,4E,6Z,8E) or all-trans,

and the proviso that when R2 is formula II, and R1, R4, R9 and R12 are all CH3, and R3, R5, R6, R7 and R8 are all H and R11 is an alcohol group, the configuration is not all-trans.

5. Use according to claim 1 or 4, wherein the at least one compound comprises a retinoid, preferably a compound of the formula V:



(formula V)

wherein the configuration of the four isoprenoid units is all trans (E) or one or more is cis (Z).

6. The use of claim 5, wherein the configurations around the carbon-carbon double bands are all-trans (2E,4E,6E,8E) or 9-cis (2E,4E,6Z,8E), or 11-cis (2E,4Z,6E,8E), or 13-cis (2Z,4E,6E,8E).

7. The use of claim 5 or 6, wherein R3 is H.

8. The use of any of claims 5 to 7, wherein R4 is CH3.

9. The use of any of claims5 to 8, wherein R5 is H.

10. The use of any of claims 5 to 9, wherein R6 is H.

11. The use of any of claims 5 to 10, wherein R7 is H.

12. The use of any of claims 5 to 11, wherein R8 is H.

13. The use of any of claims 5 to 12, wherein R9 is CH3.

14. The use of any of claims 5 to 13, wherein R10 is CH3.

15. The use of claim 5, wherein R5 is O and R6 is a bond to R5.

16. The use of claim 5, wherein R3 is H and R4 is CH3, and R5 is O and R6 is a bond to R5, and R7 is H, and R8 is H, and R9 is CH3, and R10 is CH3.

17. The use of claim 5, wherein R3 is H, and R4 is CH3, and R5 is H, and R6 is H, and R7 is methoxy, and R8 is CH3, and R9 is CH3, and R10 is H.

18. The use of any of claims 5 to 17, wherein R11 is selected from the group consisting of:

-COOH,

- an alcohol group, such as -CH2OH,

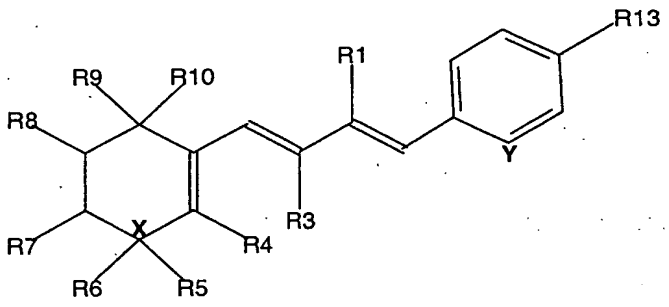
- an aldehyde group, such as -CHO,
-CH2OCOCH2Br,
-CH2OCOCH2Cl,
-COOCH2CH3,
-CONHR, wherein R is preferably 4-hydroxy-phenyl or ethyl, and
-COOR, wherein R is beta-D-glucuronide.

19. The use of any of claims 5 to 18, wherein R1 is CH3.

20. The use of any of claims 5 to 19, wherein R12 is CH3.

21. The use of claim 1 or 5, wherein the at least one compound comprises a compound selected from the group consisting of: isotretinoin (13-*cis*-retinoic acid), 11-*cis*-retinol, 11-*cis*-retinal, 11-*cis*-retinyl bromoacetate, acitretin, etretinate, fenretinide, 4-oxo-isotretinoin, motretinide, retinaldehyde, *all-trans*-retinyl bromoacetate, *all-trans*-retinyl chloroacetate, and retinoyl betaglucoronide.

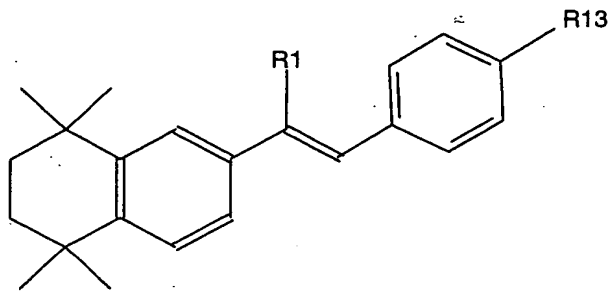
22. The use of claim 4, where the compound has the formula VI:



(formula VI)

23. The use of claim 22, wherein R3 and R4 are both CH and are connected by a double bond.

24. The use of claim 23, wherein the compound has the formula VII:



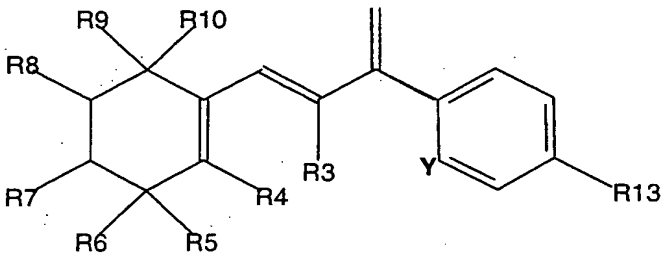
(formula VII)

25. The use of claim 24, wherein R13 is selected from the group consisting of: a carboxy (COOH) group, an ethyl sulfone group, and an ethyl ester group.

26. The use of claim 24 or 25, wherein R1 is CH3.

27. The use of claim 1 or 24, wherein the at least one compound comprises a compound selected from the group consisting of: arotinoid ethyl ester, arotinoid-free carboxylic acid and arotinoid ethyl sulfone.

28. The use of claim 4, wherein the at least one compound has the formula VIII:



(formula VIII)

29. The use of claim 28, wherein R3 and R4 are both CH and are connected by a double bond.

30. The use of claim 28, wherein R4 is CH and R3 is CHRCH3, wherein R is a double bond to R4.

31. The use of any of claims 28 to 30, wherein one or more, preferably all, of R5, R6, R9 and R10 are CH3.

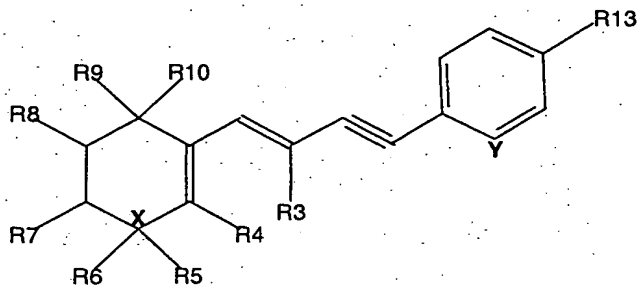
32. The use of any of claims 28 to 31, wherein R7 and R8 are both H.

33. The use of any of claims 28 to 32, wherein Y is C.

34. The use of any of claims 28 to 33, wherein R13 is a carboxy group.

35. The use of claim 1 or 28, wherein the at least one compound comprises bexarotene.

36. The use of claim 4, wherein the at least one compound comprises a compound of the formula IX:



(formula IX)

37. The use of claim 36, wherein R3 and R4 are both CH and form a double bond.

38. The use of claim 36, wherein R4 is CH and R3 is CHRCH3, wherein R is a double bond to R4.

39. The use of any of claims 36 to 38, wherein R9 and R10 are both CH3.

40. The use of any of claims 36 to 39, wherein R7 and R8 are both H.

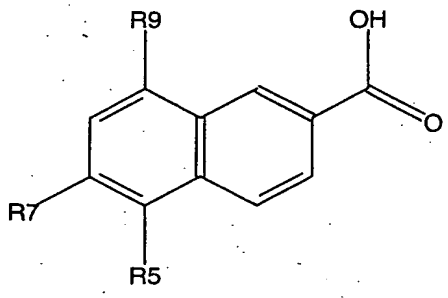
41. The use of any of claims 36 to 40, wherein X is S and R5 and R6 are absent.

42. The use of any of claims 36 to 41, wherein Y is N.

43. The use of any of claims 36 to 42, wherein R13 is a alkoxycarbonyl group, preferably an ethoxycarbonyl group.

44. The use of claim 1 or 36, wherein the at least one compound comprises tazarotene.

45. The use of claim 4, wherein the at least one compound comprises a compound of the formula X:



(formula X)

46. The use of claim 45, wherein R5 is H and R9 is H.

47. The use of claim 45 or 46, wherein R7 is 3-(1-adamantyl)-4-methoxyphenyl.

48. The use of claim 1 or 45, wherein the at least one compound comprises adapalene.

49. The use of any of claims 1 to 3, wherein the at least one compound is DAPP.

50. Use according to any of the preceding claims, wherein the at least one compound is composed as a pro-drug.

51. Use according to any of the preceding claims, wherein the medicament is in a form for being administered locally.

52. Use according to claim 51, wherein the medicament is in a form for being administered intravitreally.

53. Use according to any of the preceding claims, wherein the medicament is in device formulation held confined by mechanical or physico-chemical effects.

54. Use according to any of the preceding claims, wherein the medicament is in a slow-release formulation.

55. A pharmaceutical composition suitable for intravitreal implantation comprising a pharmaceutically effective amount of at least one compound capable of inhibiting the visual cycle and/or dark adaptation.

56. The pharmaceutical composition of claim 55, wherein said pharmaceutically effective amount of said at least one compound is determined by measuring the level of reduction of dark adaptation in a treated subject.

57. The pharmaceutical composition of claim 55 or 56, wherein said pharmaceutical composition is in device formulation held confined by physico-chemical effects.

58. The pharmaceutical composition of any of claims 55 to 57, wherein said at least one compound comprises a compound having at least one feature according to any of claims 2 to 54.